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12-14 on May 1959 in Liblice there was a symposium on the "Pharmacology of Nerve Stimulation" which was arranged by the pharmacological committee of the Physiological section of the Czechoslovak Medical Society named after J. E. Purkynve. Foremost workers in the field took part in this symposium. They were from the USSR (Anickov, Zakusov, Mirzojan) and the peoples' democracies, East Germany (Jung, Hauschild, Scheer, Sieke, Wiegershausen), Poland (Kubikowski), Hungary (Borsi, Tardosz), and the Western European nations, England (Holton, Mongar), Erance (Cheymol), Austric (Brucke, Lembeck) and Belgium (Heymans, Reuse). In addition to this a fifteen-member tourist group of young scientific workers from the USSR took part in the meetings.

The symposium was opened by Prof. Paskova and the meeting was welcomed by Academician Laufhager from the Czechoslovak Academy of Sciences. On the first day representatives of the Central Committee of the Czechoslovak Communist Party and representatives of MSVU also took place. The first day of the symposium was concerned with the pharmacology of the central nervous system.

The introductory lecture by S. V. Aničkov (Pharmacological Division of the Institute for Experimental Medicine, Leningrad) was on "Pharmacology of the Central Cholinolytic Substances", and dealt widely with new concepts in the field of these substances. The author showed that trasentine, which had previously been considered as a substance which can replace atropine, has a substantially stronger effect on the cholinerzic synapses of the central nervous system than atropine, while its peripheral effects are weaker. A whole series of esters and thioesters related to trasentine act quite similarly. The central effects were studied chiefly on the conditioned reflexes of dogs, and also through their effect on the electroencephalograms in rabbits and studying the antagonism of these substances against nicotine and arecoline, whose action is destroyed by trasentine. There also exists an antagonism between the central cholinolytic substances and anticholinesterase substances (Michelson, Paskov). The following were chiefly used: physostigmine, prostigmin, phosphacol and the alkaloid nivalin. It is interesting that beside

their depressing effect the central cholinolytic substances cause heightened activity of the center controlling the secretion of ACTH. Further the author summarized all evidence concerning the relationship between the structure and the central effect of the cholinolytic substances. For example transition to the aromatic esters of oxygenated acids increases the central effects of the esters, specifically the effect of these substances on conditioned reflexes (benactizine supresses conditioned reflexes great deal more than the unconditioned, while the transentine ester of diphenylacetic acid acts equally on both sets of reflexes). Esters of the oxygenated acids have a primarily antagonistic effect against the central effect of arecoline, while the esters of oxygenated acids which had the hydroxyl removed have a similar effect on nicotine. The increase of the central effect has also been observed when oxygen is replaced with sulphur in the esteric bond. Their characteristics are sharply altered when the tertiary amines are transformed into quaternary. This lowers the effect on the brain and increases the effect on the bulbar centers. Pharmacological followup of the effects of the central cholinolytic substances has made it possible to increase the area of their therapeutic use. (in stenocardia, spasms of the peripheral blood vessels, and bronchial asthma).

A. Zeleny and J. Kozak (Physiological Institute of the Medical Faculty of KU, Plzen) presented a report on "Relation of Acetylcholine to the Metabolism and Functional Estate of the Central Nervous System". They noticed an increase of the acetylcholine content in brains of rats after administering chlorpromazine; at the same time synthesis of acetylcholine was not affected. The hypothetical interference with metabolism, shown by lowered oxidation of glucose at several points in the change sequence, was proven even when minimal doses were given (1 to 10 micrograms/ml) On an isolated heart of a rat after administration of chlorpromazine the inversion of the inotropic effect of acetylcholine was noted, in frogs the acetylcholine pull on the m. rectus abdominis is lowered, and the action of vagus nerve and acetylcholine on the heart is blocked. The influence of chlorpromazine on the effect of acetylcholine depends on the presence of calcium ions and the sulphhydryl groups.

F. Svec and E. Hlavayova (Oncology, SAV, Bratislava) concerned themselves with the "The influence of Digitalis on the Synthesis of Acetylcholine in Vitro in a Brain Homogenate, and in an Artificial Enzyme System". By adding small concentrations of digitalized glycosides to a brain homogenate the normal aerobic synthesis of acetylcholine is increased, by adding higher concentrations it is suppressed. If acetylase obtained by drying brain cells with acetone is used digitalis has no effect; if to this cell-free enzyme system a cell suspension is added, it is possible in this case to cause an increase or suppression of the formation of acetylcholine. The authors explain this phenomenon either by an increased release of acetylcholine or even possibly an interference with its synthesis.

They state that the mechanism thus observed plays a part in influencing permeability of cellular structures and thus also cause the shift of ions, particularly potassium.

Z. Servit (Physiological Institute of the Czech. Academy of Sciences, Prague) condensed the previous experiments of his laboratory in the report on "Comparative (Phylogenetic) Study of the Effect of Certain Anti-epileptic Substances". In comparing convulsive tendencies in frogs, mice, rats and rabbits, they discovered that convulsive reactivity to a pharmacological stimulus, rises with the phylogenetic evolution of the brain. Similarly the activity of the common anti-epileptic substances rises too. In experiments on frogs they compared the effect on convulsive reactivity and on the symptomatology of of the epileptic fit, brought out by a localized transcranial electric shock, with the effect of the same antiepileptic substances in mammals. The effect of Sondanton and Dormiral within this group increases, while Trimedal does not affect the electric shock convulsions either in amphibians or in vertebrates, while it does have an effect on the pentazole convulsions. These results are significant for the solving of theoretical problems concerning the pathophysiology of the central nervous system.

E. Scheerova and E. Siekeova (Institute of Corticovisceral Pathology, Berlin) carried out electroencephalographic studies of the effect of ethylcrotylbarbiturate, a new hypnotic drug, compared to phenylethylbarbiturate. The first substance has a considerably shorter effect and the reaction of the animals to irritation with electric current is substantially different. The authors emphasize the significance of such complex study of the effect on the central nervous system, which enables one to fully explore the pharmacodynamic effect of a new drug.

M. Lukasiewicz (Pharmacological Institute of the Medical Faculty, Kosice) lectured on "Combined Relationships of Certain Drugs, both Centrally Stimulating and Depressing, to Reserpine." In experiments on mice and rats reserpine was given as premedication /predemikace/, and then the effects of subsequently administered dihydroxycodeinone, amphetamine, nikethamide and bemegride, were compared. In an experiment that was set up in the above manner- the dihydroxycodeinone lost some of its capacity as an analgesic and as respiratory depressant, but its sedative effect was enhanced; the stimulating effect of bemegride on respiration and motion is increased slightly but so is lethality; the increase of lethality was likewise observed with amphetamine and nikethamine in the early stages, and then as the effect of reserpine was developed the lethality dropped. A hypothesis was expressed about blocking the "receptors" to achieve certain effects of these drugs.

J. Sterc (Physiological Institute Czech Academy of Sciences, Prague) in his work on "Reserpine and the Convulsive Reactivity" was trying to solve the problem of the pharmacological influences on the audiogenic

epilepsy of rats.He formed a hypothesis on the basis of reports in the literature that reserpine has a depresssing effect on the cortex of the brain and a stimulating effect on the reticular formation which creates a favorable environment for the irradiation of convulsive irritation. This hypothesis was experimentally proved, with the interesting discovery that this condition persists until one can assume that the organism no longer contains even traces of the administered drug. In conditioned reflexes disturbance in the internal depression mechanism was noted, as evidenced by the negative differential stimuli coming out of the depressed state.

The lecture of J. Bures and O. Buresova (Physiological Institute of the --Czech Academy of Sciences, Prague) was on the subject of "The Use of Widening Depression as Environment for the Study of the Action of Substances with an Affinity for CNS". This was a summary of previous results of this working group dealing with widening cortical depression after direct application of chemical stimuli to the surface of the brain cortex. Thus this method is a sensitive indicator of the drugs' action on the brain cortex, with particular emphasis on the processes maintaining the integrity of the neuron cell membranes.

J. Vanecek and H. Raskova (Chair of Pharmacology and Experimental Pathology, Faculty Pediatric Division, Charles University, Prague) reported on "Effect of Intracerebral Injection of Bacterial Toxins on Behavior of cats". By using Feldberg's method of intracranial cannulae they determined the basis difference between the effect of Streptolysin O, after which they observed almost immediate choreo-athetotic convulsions, and the toxin of Shigella shigae, where the changes take place after a considerable period of latency. The character of these changes then is reminiscent of the effect caused by intracerebrally administered serotonin. Varying mutual relationship of the toxicity of these two toxins, when compared with intravenous and intracranial administration on mice, seems to testify to neurotoxicity of Streptolysin O and simultaneously deny the primary neurotoxic effect of the Shigella shigae toxin.

V. Vitek, K. Rysanek and M. Vojtechovsky (Institute for Further Education of Doctors, Prague) noted in people "Certain Metabolic Manifestations of Experimental Psychosis after Use of Benactizine". The picture resembles atropine delirium. They noted a considerable drop in the content of 5-hydroxyindoleacetic acid in urine in hourly relation to changes in the higher nervous activity, and with a simultaneous drop in the activity of monoaminooxydase and increased elimination of the 17-hydroxysteroids. The authors expressed an opinion that the psychogenic effect of Benactizine is related not only to the metabolism of acetylcholine, but also to that of serotonin.

F. Von Brucke (Pharmacological Institute of the Medical Institute,

Vienna) dealt with "The Pace-maker Zone in the Septum Pellucidum of Rabbits." His coworkers succeeded in isolating topically in the foremost part of the hippocampus a series of regular waves, observable on the EEG of the occipital cortex, on the thalamus, the septum and the dorsal and precommissural fornix during the course of the arousal reaction. Hardly noticeable lesions of the septum prevent their spreading. The arousal reaction brought forth by physostigmine can be blocked by the same action on the septum as the local application of procaine. The reactions brought about by local electrical stimulation were also noteworthy.

A. V. Valdman (Pharmacological Institute of the Medical Institute of I. P. Pavlov, Leningrad) dealt with "Pharmacology of the Reticular Formation". Important were certain variations determined in the sensitivity of the neurons of the reticular formation toward certain drugs. Using as models six kinds of experimental convulsions with the same external manifestations but with a different mechanism of origin he proved the hypothesis of the possibility of chosing drugs with a directed specific effect on the neurons of the reticular formation.

P. Kubikowski (Pharmacological Institute of the Medical Faculty, Warsaw) reported on the results of the experiments of Docent Venulet; "The Effects of Chlorpromazine and Acetopromazine on Conditioned Reflexes and their Changes after Application of Iproniazid". Both phenothiazines have a depressing effect on the defensive conditioned reflexes of rats, which had been strongly antagonized by iproniazid. At the same time the anti-serotonin effect of the phenothiazines was noted.

The second day the symposium continued to deal with the theme of pharmacology of the disturbance in the peripheral nervous system.

The first lecture by V. V. Zakusov (Institute for Pharmacology and Chemotherapy AMN USSR, Moscow) "The Influence of Pharmacological Substances on Reflexes of the Heart" described the importance of reflexogenic zones in the heart, whose irritation could be in close correlation with the pathological processes in various heart diseases. His coworker M. J. Ladinskaja dealt with the meaning of the pain syndrome for the changes in blood circulation and breathing in the presence of insufficiency of coronary circulation. She determined the influence of analgesic substances on these changes in reflexes in acute as well as chronic experiments. By using a very ingenious method on dogs, by stretching the ligature, which had been introduced under the coronary artery and then brought out to the surface of the body by a plexiglass cannula, she could cause an acute ischemia in the corresponding region of the myocardium. Ischemia brought about in this fashion could be influenced by analgesics (morphine, thecodine, promedole, phenadone) which lowered considerably and even suppressed circulatory reflexes of the respiratory changes, this was

particularly true of phenadone.

In acute situations in decerebrated cats she determined that the weakening of the heart reflexes by the analgesics does not depend on their effect on higher part of CNS, but is related to their effect on segmented divisions of the central nervous system. Likewise normalization of the EKG depends on the inhibition of the relex element of the reaction, because it was determined that the speed of the total volume of the coronary circulation is not increased by any of the substances except morphine (N. V. Kaverine) Phenothiazines, mepazine, and aminazine acted in a similar fashion, and even though they were weaker they lasted longer. It was found that the most effective was a mixture of mepazine with phenadone, since it had a stronger effect, and lasted over 48 hours. Of the other substances procaine was also found to be effective.

This reaction was further tested on the changes in chemoreceptors in the coronary circulation. Coworker I. N. Pidevic reported on influencing of changes caused by serotonin, blood serum and veratrine. The general effect was similar to ischemia, only it lasted less time and when medium doses of analgesics were administered it was only temporary. These observations could have considerable practical significance due to the fact that for example serotonin and ATP are active in the heart afflicted by an infarct of the myocardium and this fact undoubtedly plays a role in the development of pathological changes in the function of an organism. Similar results about influencing reflex changes in the pulmonary circulation were reported by Z. N. Ivanova.

N. V. Kaverina (Institute of Pharmacology and Chemotherapy, AMN USSR, Moscow) in her report "Influence of Pharmacological Substances on Reflex Reactions of the Coronary Vessels" was concerned with the mechanism of the effect of nitroglycerine and the analgesics on the blood supply of the heart muscle. The author was concerned with the controversy regarding the effect of nitroglycerin on the blood supply of the heart. Only those authors (Essex, Herrick, Baldes, Mann) who carried out their experiments by recording the blood circulation by a thermoelectric method noted considerable increase in the speed of the coronary circulation under the influence of the nitroglycerin involving the whole organism.

According to the results of investigators who had been using more thorough methods (Boyer, Green, Eckenhoff, Hafkenschiel, Kisin) nitroglycerin did not bring about any noticeable changes in the condition of the coronary vessels. The author herself used the method of measuring the resistance (change of pressure was recorded at the point where the outflow of the infusing pump enters the mouth of the left coronary artery). The reflex of narrowing of the coronary vessels was brought about by irritating the carotid sinus and electric irritation of afferent nerves. Nitroglycerin completely repressed the reflex changes of the coronary flow,

while reflex changes of the blood pressure reached as much as 50%. The hypothesis states that the removal of the pain syndrome in stenocardia by means of nitroglycerin is actually connected with improving of the blood supply of the myocardium, which, however, is achieved chiefly by suppressing the reflex spasm of the coronary vessels. It was determined that substances acting as analgesics have a similar capacity to suppress the reflex reactions of the coronary vessels however this effect is not as selective as with nitroglycerin (reaction to TK is correspondingly lowered) and it is impossible to suppress the reflexes completely with them. When higher doses are used the effect is actually reversed. The selectivity of the nitroglycerin effect give us hope that other substances might be discovered with a selective effect on the reflex regulation of circulation in other organs and organ systems as well.

The lecture of J. J. Peuse (Pharmacodynamic and Therapeutic Laboratory Med. Fac., Brussels) "The Effect of Reserpine of the Cardiovascular Reactions Caused by Sympathominetics" dealt with the effect of reserpine on a heart-lung preparation in a dog. He noted that if the material came from an animal which had 24 hours previously received intraperitoneal reserpine in the dose 0.1-0.2 mg/kg the reaction to ephedrine and to reserpine itself disappeared. Rabbits that had not been narcotized showed after larger doses of reserpine an increased reaction to adrenaling and noradrenalin, which were followed in their blood pressure and in the disappearance of their reaction to 1-1-dimethyl-4-phenylpiperazine. In rabbits and guinea pigs previously influenced with reserpine, whose isolated atria were influenced by sympathominetics, no particular changes were seen as compared to controls. When electic shock was used on the non-narcotized rabbits hypertension and tachycardia were brought about. This reaction changes strongly after administration of reserpine, in fact brachycardia and hypotension is caused.

The lecture of J. I. Vichlajev (Institute of Pharmacology AMN USSR, Moscow) "Influence of Neuroplegic Substances on Chemoreception" was concerned with influencing of the chemoreceptive zones and vessels of the rear extermity in cats. The experiments were carried out by using a donor or infusion pump on an isolated extremity with a preserved nerve connection through n. ischiadicus. The reflex changes were evoked by acetylcholine and 10% solution of NaCl. Chlorpromazine, mepazine, propazine and etaperazine (Trylafon) were used. When irritating substances were introduced into the arterial system of an isolated extremity they were followed by a reflex rise in pressure in the recipient and lowering of pressure in the donor (this did not occur when NaCl was given). Introducing normal doses of neuroplegic substances into the circulation of the donor did not cause reflex rise of pressure in the recipient. However it was possible to remove these reflexes by introducing the substances directly into the arterial system of the isolated limb or into the circulation of the recipient. Thus neuroplegic substances do not show a notable effect on the sensitivity of chemoreceptors, in the doses that completely suppress

pressor reaction of blood ppessure of a reflexive origin. A considerable suppression of the chemoreceptors is only possible when the preparations are highly concentrated in individual regions of the blood stream, and this effect cannot be produced with the commonly used doses. This observation agrees with the work of Charkijevic and Decourt who showed that chlorpromazine when given in the usual dosage and method of administering does not block the ganglia. The author reasons that suppression of the chemoreceptors and the so-called endovasal anesthesia does play an important role in the mechanism of the suppressive effect of chlorpromazine and related substances on reflexes of the vessels.

Z. I. Vedenejeva (Pharmacological Division of the Institute for Experimental Medicine, Leningrad) presented a report on "The Effect of Neural and Humoral Factors on Appearance of Experimental Myocarditis". The author caused experimental myocarditis by high doses of adrenalin or noradrenalin and by mechanical damage of the stellate ganglion. The changes were followed by EKG and histological analyses. In the attempt to prevent damage to myocardium by using drugs she used sympatholytin, chlorpromazine, chloracizine, hexethonium, luminal, amytal, and procaine. The only substances that were effective were sympatholytin and chlorpromazine. Considering the fact that chloracizine, which has a similar structure to chlorpromazine and similar action, (however not the same sympatholytic effect) was not effective one can assume that sympatholytic effectiveness is very important for prevention of experimental myocarditis.

The lecture of A.A. Mirzojan (Chair of Pharmacology, Med. Fac., Jerevan) "The Influence of Ganglerone on the Transfer of Irritability and on the Content of SH-groups in Tissues", was concerned with the mechanism of the effect of the chloride of the alpha-beta-dimethyl-gamma-diethylaminopropionic ester of isobutoxybenzoic acid on the central and vegetative system. This substance blocks the transfer in the ganglia. This blocking action can be destroyed by cysteine, which was demonstrated in experiments using a perfused ganglium of Cervicale super.

D. A. Charkievic (Institute for Pharmacology and Chemotherapy, AMN USSR, Moscow) in his very interesting report on "Influence of Ganglioblocking Substances on the Subsequent Suppression in the Ganglia" noted the difference in the action of hexamethonium, pendiomide, mecamylamine on the one hand and TEAB on the other. He tried out the effect of these substances on the stellate ganglion, where the first group of substances caused the disappearance of the posttenatic facility, while TEAB caused its increase. The author thinks that this phenomemon depends not only on the change in sensitivity of nerve cells in the ganglia, but also on the reactivity of the presynaptic endings.

J. Vik (Physiological Institute, Med. Fac., Ku, Plzen) in his contribution "Remarks on the Method of Determining Content of Acetylcholine in the Heart and its Significance in the Action of the Heart", was concerned

with the meaning of acetylcholine for automatic heart activity. The author followed the factors which influence the amount of bound acetylcholine (probably to proteins) in the heart.

To measure the content of acetylcholine he used the improved method of Rothschuh by testing on a isolated straight abdominal muscle of a frog, which was sensitized by addition of adenosine triphosphoric acid to the bath. This addition not only increases the contractions after acetylcholine, but also prolongs the longevity of the preparation without influencing the contraction of the muscle. The author determined that in several kinds of animals (rat, dog, guinea pig) there is parallel between the content of acetylcholine in different parts of the heart and the so-called automation gradient (Gaskell) that is places with the highest automation contain the highest amount of acetylcholine. Further he observed an increase in the content of acetylcholine in the heart in the first months after the birth of the dogs. Again the highest increment was in those regions of the heart which had the highest automation.

N. V. Visockaga (Institute of Pharmacology and Chemotherapy AMN USSR, Moscow) in her report "The Influence of the Ganglio-blocking Substances on the Metabolic Processes in the Vegetative Ganglia" concerned herself with the metabolism of phosphorus in the ganglion cervicale super, where the blockade by nicotine, pendomide and pachycarpine was combined with lowering of ATP and creatine phosphate in the ganglion. Hexamethonium did not have this effect. Further studies showed that both the activity of ATP is heightened and the content of glycolase is increased. Thus it seems that the effect of hexamethonium in contract with the other tested substances does not depend on the changes in the phosphorus metabolism.

O. Gulda (Chair and Pharmacology, Fac. of Pediatric Medicine, Charles U, Prague) described in his lecture "Changes in the Reactivity of the Organism to TEAB after a Laparotomy" his observations on anaesthetized cats where he determined that a laparotomy substantially changes the response of the organism to administration of TEAB. The main change was in the reaction of the nictitating membrane following a preganglion irritation of the sympathetic nervous system of the neck, and in the changes of the reaction of blood pressure particularly of the quantitative type. Phase reactions were also noted.

V. Trcka (VUFB, Prague) described the characteristics of three new types of ganglioplegic substances, as follows: 2-dimethylaminoisocamphane (dimekamine), trin/sic/ethylcyclohexyldimethylamine (penhexamine) and 2-dimethyl-amino-2,3,3-trimethylbutane(penbutamine)synthetized at the VUFB with low toxicity and administered orally. He showed that the cyclical nucleus is not a necessary condition for activity of the tertiary amines. These substances are at the present time being clinically tested.

The afternoon session was opened with a lecture by C. Heymans winner of the Nobel prize for his work on the physiology of the carotid sinus (Pharmacological Institute of the Medical Faculty, Ghent). The subject of his lecture was "The Cardiovascular and Pulmonary Reflexogenic Areas". The baroreceptors of the nerve endings, which are concerned with maintaining blood pressure, are in the arc of the aorta and the region of the carotid sinus. These receptors are sensitive to the pressure of the arterial wall, within which they are contained. The presence of baroreceptors was demonstrated in other areas as well, which have a primary significance in reflex adaptations of local character. It seems that the most common effects on the cardiovascular system are produced on the receptors in the atrium of the heart, in the venae cavae, and in the pulmonary circulation. These receptors influence the adaptation of the venous return of the blood volume and also the heart beat. Chemoreceptors sensitive to the physiological composition of blood and to pharmacological stimuli are located in the aorta and the carotids. Irritation of these receptors evokes specific and non-specific circulatory and respiratory reflex reactions. Current experimental material is not too convincing about the existence of chemoreceptors in other areas. Perhaps in the future specific chemical stimulants will be discovered for them.

Mr. and Mrs. Gerovy (Institute for Experimental Medicine SAV, Bratislava) gave a very interesting lecture on the meaning of frequency and amplitude of pulsation in relation to irritation of receptors in the carotid sinus. They concentrated on the question of the mechanism of the irritation of baroreceptors and the related question of the elasticity of the blood-vessel wall. Very ingenious experimental work of both the authors brought proof of the significance of pulse frequency and threw new light on the importance of this parameter for evoking a reflex response. Further the authors followed, in varying hemodynamic situations, the mutual relation of the pressure and volume oscillations, as an indication of the elasticity of blood vessel wall in sinocarotid area in situ and in vitro. They interpret the differences that they determined in the stretching of the blood vessel wall (on the one hand in the "stimulus" phase, on the other in the "regulation" phase during a cardiovascular reaction) from the standpoint of the influence on the liquidation of given hemodynamic situations.

S. S. Krylov (Institute of Experimental Medicine, Pharmacological Div., Leningrad) lectured on "Pharmacological Analysis of the Sensitivity of Receptors in the Sinus Caroticus". He determined that the sensitivity of the sinus, influenced by acetylcholine, remained unchanged after treatment with nicotine and sodium cyanide, while after treatment with nicotine the response of the chemoreceptors to acetylcholine is missing, parallel to unchanged response to sodium cyanide. After treatment with sodium cyanide the area is no longer sensitive to any other stimuli. Likewise the electrical activity of the appropriate nerve is completely

suppressed. The author reasons that the acetylcholine stimulus and the stimulus after treatment with sodium cyanide evokes different reactions in the CNS. For example he noted that after acetylcholine stimulus there is reflex contraction of the intestines, while after sodium cyanide there is a relaxation.

The extensive lecture of J. Cheymol (Pharmacological Institute of the Med. Fac., Paris) was on the subject of "The Excitability of the Motor Barrier". It dealt with structures and phyisiological mechanism of the neuromiscular synapse. First he presented the review of recent work on the motor barrier by means of an electron microscope. The following factors chiefly affect the main anatomical structures: the nerve, the motor barrier and the muscle and these are acetylcholine, potassium ions, and electric stimuli. Further the author explained various ways of action by curare-like substances. Then he related the activity of these substances to their chemical structure.

V. M. Karasik (Institute of Experimental Medicine, Leningrad) reported on "Differentiation of the Structure of Skeletal Muscles, Reacting to Potassium Ions and to Acetylcholine" and showed that different groups of drugs (substances which block the sulfhydryl groups, substances which influence phosphorylation, and narcotics) can affect in different ways the reaction of the musculus rectus of a frog to potassium ions and to acetylcholine. The author hypothesizes that different structures which participate in transfer of the nerve stimulus react either to the potassium ions or to the acetylcholine.

V. Grossmann (Pharmacological Institute Med. Fac., Ch. Univ., Hradec Kralove) presented "Contribution to the Clarification of the Relationship between the Central and Peripheral Effects of Certain Myorelaxing Substances". His report dealt with the capacity of the central tubarine and decamethonium. By analysing the relation of both substances to strychnine in mice it was determined that an antagonism exists between strychnine and tubarine, while between strychnine and decamethonium there is synergy. Experiments were carried out in which the effect on the latent period -- according to Zakusov's method -- was tried using both substances in rabbits both normal and myelotomized. Since decamethonium, which increases the effect both with a weakened and heightened influx of stimulation, loses its effectiveness considerably after a myelotomy, the author thinks that what occurs is a change in the sensitivity of the neuromuscular connection. When tubarine is used the weakened effect in the first phase can be brought about by removal of the active depressant, evoked by irritation of the central nervous system. In higher doses it overcomes the depressant and thus the increase of its effect by influencing the blockade of the spinal-cord synapses.

E. V. Moreva (Institute for Experimental Medicine, Pharmacological

Division, Leningrad) reported on the pharmacological influence on the changing sensitivity of the muscle to potassium ions. She showed that anaesthetics can completely suppress the effect of potassium ions on muscles. And, dinitrophenol, e.g., sensitizes the muscle to these effects. It is interesting that reactivity to acetylcholine is not influenced by anaesthetics. This suppression of the synaptic component of the potassium effect by narcotic substances may play an important role in the mechanism of the effect of the narcotic substances.

Z. Finek and M. Sajda (Military Research Medical Institute, Hradec Kralove) lectured on "The Mechanism of the Antiacetylcholine Effect of Certain Substances" and reported on experiments on the ileum of a guinea pig, and on the attempts to synthesize acetylcholine in the organism following administration of a series of substances with an antiacetylcholine effect. They selected for testing certain tertiary and quaternary basic nitrogenous esters of substituted acetic acids and also the preparation Artan. They determined that some of these substances affect the action of free acetylcholine, while others do not have this effect but do strongly inhibit the synthesis of acetylcholine (pyridin-2-aldoxime-methiodide).

F. V. Selecky, L. L. Vrbovsky and L. Rosival (Pharmacological Laboratory of the Chemical Institute SAV, Bratislava) reported on the non-specific effects of certain organic phosphates. Dipterex, phosphothione, melathione, ecatine, dimethyldichlorovinylphosphate and timet were followed in chronic experiments lasting 10 weeks, and also in acute ones. Toxicity in different kinds of animals and percutaneous activity were determined.

The closing lecture was by M. Bargar (Pharmacological Institute of the Med. Fac. Bratislava)" Myoneural Activity of Certain Derivatives of Basic Isopropanols". He evaluated new synthetic substances, from the viewpoint of myorelaxing effect on an isolated diaphragm and on a preparation of ischiadicus-gastrocnemius in cats. He determined that these substances cause paralysis of the extremities much sooner than paralysis of respiration. This paralysis is freed by syntostigmin and TEAB. These substances are effective in doses from 10-20 mg. /kg/

The third day of the symposium, concerned with the pharmacology of nerve mediators, focused its attention of reports dealing with several newly discovered substances, whose function in the nervous system is not entirely clear. Thus in the opening lecture by F. Lembeck (Pharmacological Institute of the University, Graz) was on "Localization of the P Substance in the Central Nervous System" and presented a combined summary of great many experimental results, both his own and foreign. Detailed analysis of the cholinergic transfer of stimulation showed that alongside of cholinergic neurons there are also "non-cholinergic" neurons, to which belongs, for example, the first sensitive suron, the pyramidal path, and

the nervus opticus. Stemming from a whole series of observations on the P substance some tend to believe that this substance could be this very humoral tranferrant, while others are opposed to this theory. Both in the cerebrum and in the cerebellum there is a small quantity of the P substance; mesencephalon, extended spinal cord, fasciculi and nuclei gracilis a cuneati, grey matter of the spinal cord, the retina and particularly the area postrema all contain high amounts of the P substance. Contrasted with this there are small amounts in the pyramidal path, in the bulbus olphactorieus and nervus opticus. In the peripheral nerves the dorsal roots of the spinal cord contain 5-10 times more P substance than the ventral. Also a greater amount is contained in the truncus sympaticus, medium amount in the nn. ischiadicus and saphenus, little in acusticus, phrenicus and splanchnicus. Comparison of the contents of this substance in other animals showed that phylogenetically older parts of the CNS contain more P substance than the phylogenetically younger ones. Tumors from tissue with gliosis or immature cellular elements did not contain a significant amount of P substance. By fractionation of the cellular elements in an ultracentrifuge it was shown that the highest amount of P substance (combined with nitrogen) is contained in the granular fraction. Thus it appears that similarly to serotonin, adrenalin and noradrenalin it is bound to definite cellular structures. The amount of P substance in the brain can be influenced by various drugs. Drugs with irritating effect increase its content, narcotics lower it (Zetler, Ohnesorge). Retina of the eyes that were closed 2 hours before the animals were killed, contained more P substance, however in animals that were kept in the dark the content was less (Kocic-Mitrovic). Upon denervation the amount of P substance in the nerve was less. (Holton) By following the effect of the P substance on the action of different drugs it was determined that it suppresses the irritating effect of harmine, strychnine, picrotoxin, and pervitin, similarly it suppresses convulsions after tetanotoxin, it does not influence electric shock, or the effect of cardiazol and nicotine (Sterm, Zetler). In addition it has certain anatagonistic effect toward morphine (Zetler). Stern noticed considerable similarity between the effect of P substance and mephenesine and designated P substance as a "physiological tranquilizer". Intravenous injection of this substance in people did not evoke any central effects. (Liljedahl, Mattson and Pernow) On spinal cats there was no proved effect on the spinal cord reflexes (Kissel, Domino), however some authors see a depressing effect of the P substance on the polysynaptic reflexes (Stern). After injection into the a. carotis one can note "arousal reaction" on the EEG (Lechner, Lembeck) Injection into the side chamber of the brain led to noticeable motor calming down of the cats (Fuler, Pernow). On the peripheral endings of the afferent nerves in a perfused rabbit ear the P substance caused reflex hyperventilation and a drop in pressure (Lembeck). The author emphasized that in spite of a large number of experimental results only future experiments will enable us to form a clear idea of the physiological significance of the P substance.

The second report by P. Holton (Physiological Institute of the Med. Fac., St. Mary's Hospital, London) "The Probable Role of the P Substance and ATP in the Chemical Transfer from Nerve Endings" is thematically closely related to the first one. By comparing P substance and ATP with acetylcholine one can conclude, that P substance can be the transferring agent just like acetycholine while ATP cannot even though it is released when the nerve is irritated. In experiments with a perfused rabbit ear the author showed that ATP was present in the perfusate, if sensitive nerves were irritated. This depended on the capacity of the nerve to take the disturbance and on whether the release did not take place after the degeneration of the nerve. ATP is released at the nerve endings not on the axons themselves, because during the irritation of a part of a perfused ischiadicus, which did not contain any nerve endings, it was impossible to demonstrate any ATP. ATP is likewise released from the sympathetic ganglia during irritation of the preganglionic nerve. These results show that release of the ATP is not a specific characteristic of the sensitive neurons, but of the others as well. Most likely it is at least in part the cause of antidromal vasodilation. The substance was determined in normal and degenerating nerves. Its concentration dropped in degenerating sensitive nerves as compared to a contralateral control. The same results were achieved for the axons of the primary afferent fibers of the posterior parts of the spinal cord. These results testify to the fact that P substance (or its precursor) is formed within the nerve cell and moves in the direction of the nerve endings. This was proved by determining the presence of this substance in the proximal stumps of the severed nerves, in which an increase in the amount of P substance was noted in the first few days after they were severed. This behavior, which is similar to the behavior of cholinacetylase, cholinesterase, and acetylcholine (McIntosh, Hebb and Waites, Sawyer, Cavanagh, Nachmansohn et al.,) supports the theory that P substance is an analogue of acetylcholine. Preliminary observations showed that this substance is bound in the nerve cells in particles of the magnitude of mitochondria. Thus even in this way it resembles acetylcholine and noradrenalin. In conclusion the author expressed an interesting opinion that the carriers of all types are bound in the nerve cells in particles together with ATP and if during transfer of a stimulus the carrier is released then ATP is released as well. Even though one cannot consider this view as a proven theory, it might be useful as a working hypothesis for further experiments.

The report of R. Capek (Pharmacological Laboratory CSAV, Prague) dealt with a comparison of the action of two biologically active peptides of the P substance and bradykinine. The author followed the effect on the irritability of an isolated nervus ischiadicus in a frog, of rhythmical irritation by right-angle pulse of varying frequency and duration. During slow frequency both substances raise the threshold, not directly in ratio to the length of the duration of the stimulus. Dependence of the increase of the substances on frequency was different for each of the substances. While bradykinine raised the threshold equally at all frequencies, P

substance definitely raised the threshold at high frequencies. Further the influencing of the convulsive effect of pentazole by both the substances was studied. While previous application of bradykinine lowers the ED_{50} of pentazole, a previous application of the P substance increases it. The author explained that the disagreement with previous findings in the literature, that is that the P substance does not influence the convulsive effect of pentazole (Zetler and others) can be explained by a different method of application and by a different evaluation of the effect. Further he pointed out how complex is the analysis of the effect of substances such as these peptides, which has such many-faceted central and peripheral activity.

O. Benesova (Pharmacological Institute Med. Fac. Hygiene KU, Prague) presented a report on "Effect of ATP on the Central Effects of the Barbiturates" She followed the length of thippental anesthesia by checking the straightening reflex in rats, and the depth of anesthesia in rabbits with imbedded epidural electrodes, by determining the motor threshold following application of ATP. ATP shortens and lightens the anaesthesia, if it is administered 20-25 minutes before thiopental. These findings testify on behalf of Quastel's hypothesis that the mechanism of the action of anesthetics depends on the inhibition of splitting of glucose at a certain step. This causes a considerable lowering of the formation of macroergic phosphate compounds and synthesis of the bound acetylcholine. Thus increased presence of ATP lowers the effect of the anesthesics. The objection that here we are dealing with a increased detoxication of thiopental in the liver (which requires macroergic compounds)can be countered by the fact that simultaneous or subsequent application of ATP produces no effect, while with the detoxicating mechanism it is still effective.

The lecture of J. L. Mongar (Pharmacological Institute of the University, London) dealt with "Mediators of the Allergic Reactions". In his experiments the author used isolated tissue, in order to eliminate the participation of the nervous system in allergic reactions, since he thinks that simple cellular mechanisms are the basis of allergic reactions in the whole organism and are merely modified by the nervous system. He visualizes the allergic reaction as a series of steps, according to the following scheme:

1. antibodies + cells → sensitized cells
2. antigen + sensitized cells $\xrightarrow{Ca^{++}}$ activated enzyme system (tissue complement)
3. enzyme + bound histamine → free histamine
4. histamine + receptors → contraction of the smooth muscle, etc.

In 1. In order that sensitization take place the circulating antibodies must be fixed on the cells. Particularly important is their fixation on the fatty cells which contain the largest amount of tissue histamine. The reaction of the antibodies with the cells is specifically inhibited

by "non-antibody gammaglobulin", which competes with the antibodies in its fixing on the cells. Warm temperature is likewise very important for the occurrence of this fixation.

In 2 and 3. When the antigen reacts with the fixed antibodies, an intracellular process takes place, which to some extent resembles the activation of complement in serum. An enzyme reaction starts, which requires the presence of Ca^{++}. This reaction leads through hitherto unknown steps to the release of histamine which is bound to the intracellular granules of the fatty cells and other active substances. It was possible to show a significant lowering in the number of metachromatic granules in the fatty cells a few minutes after addition of antigen. Certain inhibitors, for example phenol, make desensitization possible without the release of histamine, probably by preventing the effect of the enzyme, but not its activation and subsequent inactivation. The effect of warmth and pH on this mechanism is similar to the effect on the enzyme system. After the muscle is warmed at 44° for 15 minutes it is impossible to evoke an anaphylactic reaction, even though the muscle remains sensitive to histamine.

In 4. The allergic reaction is mainly caused by substances which are released from tissues. Histamin is released not only from sensitized guinea pig tissue, which was used for the experiments, but also from pieces of human asthmatic lung tissue, when placed in contact with a specific antigen. Thus the author reasons that there is a great similarity between the reaction of human asthmatic bronchi and a isolated sensitized smooth muscle of a guinea pig to an antigen. However one cannot ascribe all effects to histamine, since beside it the "slow-reacting substance" is released as well, which also contributes to the bronchoconstriction.

The report of H. Raškova and J. Vaneček (Chair of Pharmacology and Experimental Pathology Fac. Ped. Med. Charles U., Prague) dealt with "Release of Products in Intracerebral Administration of Bacterial Toxins" and was thematically closely related to the report of these authors on the first day of the symposium. Typical changes in behavior in non-narcotized cats after intracerebral administration were brought about as well by the streptococcal toxin Streptolysin O. It had been shown earlier that this toxin produces after a prolonged latent period a slow contraction of an isolated uterus of a rat. Since in both cases the cause could be the release of active substances from tissues, the relation of this toxin to brain tissue was studied. In cats a perfusion of the liquor cavities /Zones/ according to the method of Bhattachary and Feldberg was tried. The perfusate was tested on an isolated rat uterus in an atropine solution of de Jalon and then chromatographically measured. Samples taken immediately post-operatively caused a contraction, and after 40-50 minutes were inactive. After application of Streptolysin O myotrophic activity appeared

anew. The contraction was not brought about either by histamine or by acetylcholine or serotonin, because it could not be blocked by specific antagonists of these substances. Myoactive samples likewise showed changes in the chromatograms, by appearance of a ninhydrin positive spot, which had not been present either in Streptolysin alone or in the liquor. The character of the contraction testified to the possibility that the "slow contracting substance" might be released. The fact that the release takes place even after postoperative trauma reminds the author of the work of Fine and others concerning the irreversible stage of haemorrhagic shock. Specificailly these authors prove that irreversibility is caused by departure of the bacteria from the intestines. However, it is also possible that both the trauma and the bacterial toxins release active substances in the body which are responsible for the irreversibility of shock. Some recent experiments testify to this thought indirectly in trying to increase the resistance of mice to bacterial toxins by repeated administration of phenol or repetition of the Collip shock. The author noted that her results do not warrant more concrete conclusions.

I. S. Zavodskaja (Pharmacological Institute of the Institute of Exp. Med., Leningrad) reported on "Role of Nerve and Humoral Factors in Producing Experimental Stomach Ulcers". It dealt with the author's own method of producing stomach ulcers in rats by a mechanical traumatization of the duodenum, which consisted of applying pean for 10 minutes. This procedure could, besides others traumas, also lead to increased secretion of ACTH and because of this to increased production of the corticosteroids, which could play an important part in causing the ulcers. Thus the author followed the Vitamin C level in the adrenals after her procedure, and showed that even in 2 hours it was lowered. This effect was not produced in hypophysectomized animals. However, since ulcers can be produced in both hypophysectomized and epinephrectomized animals, the hypophysoadrenal system does not play the decisive role in their formation. Even the role of histamine is not decisive, since production of ulcers can be prevented by ganglio-blocking substances and subdiaphragmatic vagotomy. These results testify that the chief cause for the production of ulcers is the reflex change in the trophic quality of the stomach wall, evoked by the traumatization of the duodenum.

Z. Votava (VUFB, Prague) reported on "Antiserotonin effect of the derivatives of the diethylamide of lysergic acid". He dealt with cyclopropyl, butyl, pentyl, hexyl, and heptylamide of lysergic acid. Their antiserotonin effect was followed on an isolated rat uterus, on isolated strips of rat duodenum and on serotonin buds that were produced in rats. Even when certain difference in the antiserotonin effect were apparent depending on the method used, it is possible to say that the original derivatives of lysergic acid showed that the antiserotonin effect declined as the cyclical nucleus increased. However all these substances were considerably weaker than LSD. Antiserotonin effect is also possessed by ergometrine, and by chlorpromazine which has quite a high effect in doses

of 40x higher. Of the whole series of synthetically prepared derivatives of lysergic acid only LSD has psychogenic effect, while a whole series of other effects is common to all these substances. Thus it seems that LSD has in this direction a specific effect on the higher nervous activity of man.

The report of V. Troka (VUFB, Prague) "A Structural Analogue of Reserpine" was Concerned with the Relation Between Chemical Structure and Pharmacodynamic Effect of Certain Structural Analogues of Reserpine". The many-faceted effects of reserpine force us to pose the question as to whether its effect is bound up with the whole molecule in its spatial arrangement, or just with a certain part of the molecule. From the many derivatives prepared by Protiva and Co., the author compared certain derivatives of 1,2,3,4-tetrahydronorharmmare in their centrally depressant effect, by using the test of a rotating stake(?) in mice and by measuring the hypotensive effect on cats. Tetrahydronorharmane alone has a weak centrally depressing and hypotensive effect. Its 1-benzyl derivative has both these effects in a much greater measure, 1-methoxy derivative is on the contrary less effective and more toxic. 2-benzyl derivatives do not have a depressant effect, while effect on blood pressure remains unchanged. A clinical check on this showed that 1-bezyl derivative (phenoharmane) has a tranquillizing effect. Hkwever the effect on blood pressure in hypertensive patients was not sufficient. Another part of the reserpine molecule is represented by the trimethoxybenzeoic ester of N-methyltryptaminoethanol and further alcohols. The first of the homologues has a depressant effect, while the blood pressure is noticeably elevated. With the lengthening of the alkyl chain the central depressant effect drops and the effect on blood pressure distinctly turns hypotensive.

The next report by A. Dlabac (VUFB, Prague) "Phenoharmane", completed the preceding with an attempt to analyse the effects of one of the derivatives of harmane. Since the effects of reserpine are closely related to those of serotonin, the author followed the elimination in the urine of dogs of the final metabolite of serotonin, 5-hydroxyindole# acetic acid, after administration of phenoharmane and reserpine. Following both substances there is an increase in the elimination of 5-hydroxyindole acetic acid in the urine, however it is less pronounced with phenoharmane. Reserpine and phenoharmane cause general depression and ptosis of the eyelid in mice. If inroniazid (Marsilid) is given, the substance which blocks monoaminooxydase and thus prevents oxidation of serotonin, then the effect of phenoharmane disappears and the onset of the effect of reserpine is put off, occasionally even excitation and exophthalmos is brought about. Qualitative differences between reserpine and phenoharmane are noticeable only in higher doses, when the reserpine effect is deepened while phenoharmane rather causes excitation similar to the effect following administration of 5-hydroxytryptophane. The experiments described above testify to similarity of the effect of these two substances and the similar mechanism of interference in relation to serotonin.

The participants in the symposium exchanged views in rich and lively discussions concerning the newest concepts in the field of neuropharmacology. The hospitable environment which enabled all participants to have uninterrupted personal contact helped in establishing personal contacts and in exchanging experiences of the individual European work-centers. The guests particularly valued the organizational aspect, where the only drawback was an imperfect translating service.

Professor Heymans, the chairman of the international physiological and pharmacological society, in his closing speech recommended setting up similar symposia in other European states, which would be one of the main tasks of a new European Pharmacological Society, which he proposed. Tightening of the friendly and scientific contacts of the participating scientific work-centers is surely a significant stimulus to world cooperation.

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